

# Histopathologic Findings of Cutaneous Hyperpigmentation in Addison Disease and Immunostain of the Melanocytic Population

Angel Fernandez-Flores, MD, PhD\*†‡ and David S. Cassarino, MD, PhD§

**Abstract:** The histopathological features of cutaneous hyperpigmentation in Addison disease have very occasionally been reported, and they include acanthosis, hyperkeratosis, focal parakeratosis, spongiosis, superficial perivascular lymphocytic infiltrate, basal melanin hyperpigmentation, and superficial dermal melanophages. We present a study on 2 biopsies from the arm and the thigh in a 77-year-old woman with a long clinical history of Addison disease as well as senile purpura and alopecia of female pattern. The patient presented diffuse hyperpigmentation of the skin, more pronounced on her face, and left upper forehead. The skin biopsies showed no remarkable dermal inflammatory infiltrate with melanocytic hyperpigmentation of the basal layer of the epidermis as well as a mild amount of melanophages in the papillary dermis. In addition, we found lipofuscin in the luminal pole of the secretory epithelium of the eccrine glands. In the perieccrine areas, there was Perls-positive pigment in the cytoplasm of macrophages most likely related to the senile purpura. An immunohistochemical study with Melan-A showed a melanocyte/keratinocyte ratio of 1:20 (5%) in the arm and of less than 1:50 (only 2 melanocytes in the whole section; <2%) in the thigh.

**Key Words:** Addison disease, hyperpigmentation, melanin, melanocytes

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## INTRODUCTION

The histopathological features of cutaneous hyperpigmentation in Addison disease have been very occasionally reported.<sup>1,2</sup> Such changes include acanthosis, hyperkeratosis, focal parakeratosis, spongiosis, superficial perivascular lymphocytic infiltrate, basal melanin hyperpigmentation, and superficial dermal melanophages.

In addition, nail hyperpigmentation has been occasionally reported as a consequence of Addison disease, mostly in the form of longitudinal melanonychia.<sup>3–6</sup>

From the \*Department of Cellular Pathology, CellCOM-SB Group, Servicio de Anatomía Patológica, Hospital El Bierzo, Cellular Pathology, Ponferrada, Spain; †Department of CellCOM-SB Group, Biomedical Investigation Institute of A Coruña, CellCOM-SB Group, A Coruña, Spain; ‡Department of Cellular Pathology, Hospital de la Reina, Cellular Pathology, Ponferrada, Spain; and §Department of Dermatology, Los Angeles Medical Center (LAMC), Southern California Kaiser Permanente, Los Angeles, CA.

The authors declare no conflicts of interest.

Reprints: Angel Fernandez-Flores, MD, PhD, Servicio de Anatomía Patológica, Hospital El Bierzo, Medicos sin Fronteras 7, 24411 Ponferrada, Spain (e-mail: dermatopathonline@gmail.com).

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Herein, we report a case in which the histopathological features of cutaneous hyperpigmentation due to Addison disease could be studied and we described some additional findings to the ones already presented in the literature.

## CASE REPORT

A 77-year-old woman came to the Dermatologist complaining of gradual scalp hair thinning with no history of increased shedding of hair.

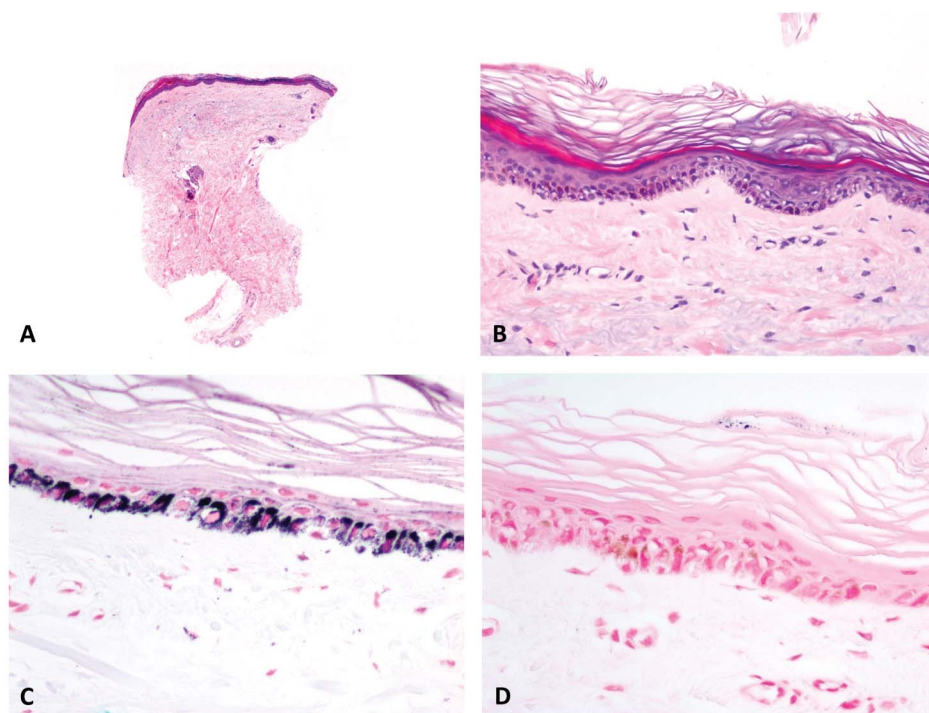
She had a known history of Addison disease, followed by endocrinology with secondary hyperpigmentation of the skin which caused her great distress. There was no history of allergies. She occasionally had taken prednisone and acetylsalicylic acid in the past that were coincidental with flat patches of purpura on her sun-exposed areas.

The examination showed mild rosacea erythema on the cheeks. The patient was using MetroCream and she was pleased with the results with no lesions noted at present. She also presented nonindurated flat patches of purpura on dorsal arms in sun-damaged skin. There was no history of gastrointestinal or genitourinary bleeding. She did not have similar lesions elsewhere on her body. These lesions occurred from time to time and spontaneously cleared. They were attributed to a senile purpura.

The examination of the scalp revealed mild hair thinning, most noticeable in the midline, with thicker density in occipital scalp, retention of frontal hair line, normal hair pull, and no discrete alopecia. She appeared well nourished and she daily took multivitamins and a diet well provided with proteins. Thyroid hormones levels were under normal limits. The diagnosis was alopecia of female pattern and 5% REGAINE as well as Biotin 3 mg was prescribed for daily use.

The patient presented with diffuse hyperpigmentation of the skin, more pronounced on her face and left upper forehead. She stated that both 4% hydroquinone and 8% hydroquinone had not helped. She had used 20% hydroquinone under the understanding that this might cause complete removal of pigment and cause white patches in her skin. So far, she had used it very sparingly and only to the areas that were most cosmetically distressing to her. She was also using sunscreen daily for other sun-exposed parts of her body. The pigmentation pattern was suspected to be related to Addison disease, but it raised the differential diagnosis with cutaneous hemosiderin deposits or pigmentation secondary to minocycline intake. Two biopsies were performed from the arm and from the thigh.

The skin biopsies showed no remarkable dermal inflammatory infiltrate (Fig. 1A). There was hyperpigmentation of the basal layer of the epidermis (Fig. 1B) as well as a mild amount of melanophages in the papillary dermis. The pigment in the epidermal and the dermal location was positive with Masson Fontana stain (Fig. 1C), whereas Perls stain failed to stain it (Fig. 1D).



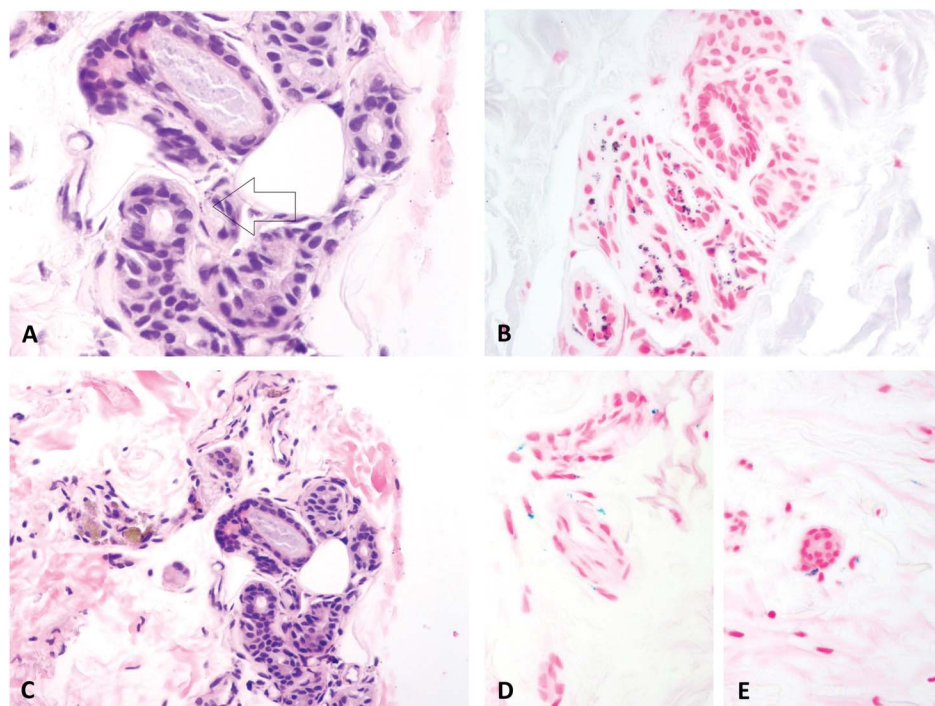
**FIGURE 1.** A, Low-power view showing no remarkable dermal inflammatory infiltrate. B, Hyperpigmentation of the basal layer of the epidermis and a mild amount of melanophages in the papillary dermis. C, The pigment in the epidermal and the dermal location was positive with Masson Fontana stain. D, Lack of staining with Perls stain.

In addition, we found granular pigment in the luminal pole of the secretory epithelium of the eccrine glands (Figs. 2A (arrow), B) that also stained with Masson Fontana and was negative with Perls stain. We interpreted such pigment as the typical lipofuscin deposits that can be found in the eccrine glands with aging.

In the perieccrine areas in both biopsies, there was a second type of pigment. It was located in the cytoplasm of macrophages and it was brownish on hematoxylin–eosin staining (Fig. 2C). This

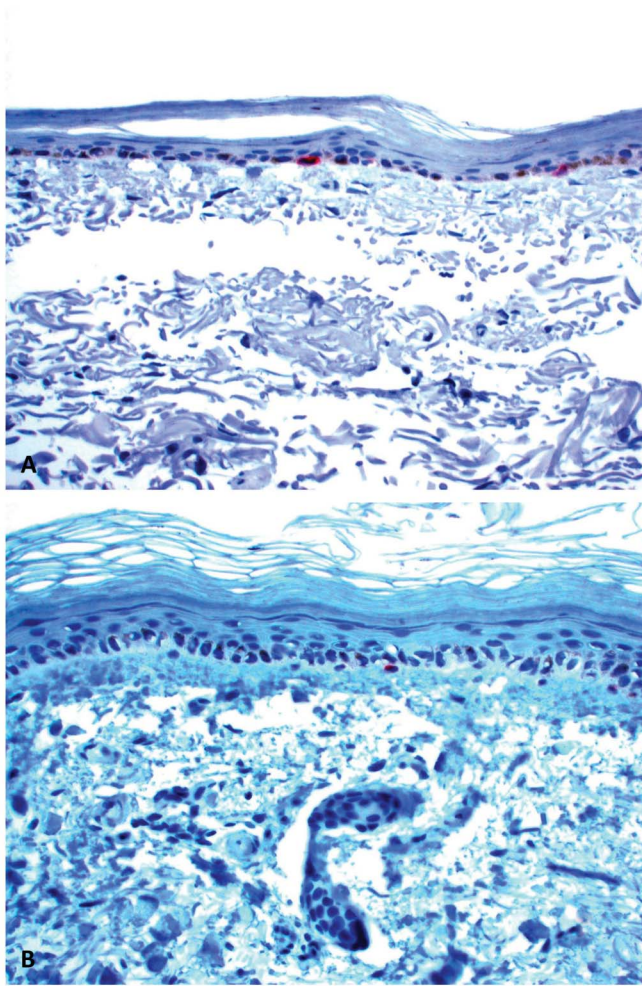
pigment was positive with Perls stain (Figs. 2D, E), and it was most likely related to the history of purpura.

We performed an immunohistochemical study with melan-A. The biopsy from the arm showed a melanocyte/keratinocyte ratio of 1:20 (5%) (Fig. 3A), whereas the biopsy from the thigh showed a melanocyte/keratinocyte ratio of less than 1:50 (only 2 melanocytes in the whole section, which equaled <2%) (Fig. 3B).



**FIGURE 2.** A, (Hematoxylin–eosin, arrow) and (B) (Masson Fontana): Lipofuscin granules in the luminal pole of the secretory epithelium of the eccrine glands. C, (Hematoxylin–eosin), (D and E) (Perls stain): Iron deposits in the perieccrine macrophages.





**FIGURE 3.** Melan-A immunostaining in the biopsies of the arm (A) and thigh (B).

## DISCUSSION

Mucocutaneous hyperpigmentation is a secondary manifestation of the Addison disease.<sup>7</sup> The hyperpigmentation can be homogeneous or blotchy, and it commonly involves the skin, oral cavity, the conjunctiva, and genitalia.<sup>7,8</sup>

Cutaneous hyperpigmentation is due to the increase in the production of the adrenocorticotrophic hormone (ACTH). ACTH acts as an agonist of the melanocortin 1 receptor (MC1-R), which is highly expressed in the surface of melanocytes. Its activation stimulates, among other things, the accumulation of eumelanin instead of pheomelanin.<sup>9</sup> ACTH is fragmented in ACTH 1-17 and alpha-melanocortin-stimulating hormone.<sup>9</sup> Both molecules share the tetrapeptide His-Phe-Arg-Trp, which is essential for melanotropic activity. However, because its production by the hypophysis is insufficient for melanogenesis, keratinocytes and melanocytes are mainly responsible for the production of such a stimulator.<sup>10</sup> In Addison disease, such mechanism is totally altered: the production of ACTH by the hypophysis is highly increased. It sounds tempting to suggest that such an abnormal scenario could result in a decrease of the number of

melanocytes, but in fact we have not found any reason that explains the low percentage of melanocytes that we observed in our biopsies.

Such hyperpigmentation is a well-known accompanying phenomenon in Addison disease, and skin biopsy is hardly ever necessary to confirm these cutaneous changes. This is the main reason why such histopathological features have very occasionally been reported.<sup>1,2</sup> In the case of Fussell et al, for instance, the biopsy was taken before the diagnostic confirmation of Addison disease.<sup>1</sup> Pramoto et al reported a case of Addison disease due to adrenal gland damage in a HIV patient in which the skin biopsy was taken at the beginning of the cutaneous darkening process because of a clinical suspicion of drug eruption.<sup>2</sup> It should also be mentioned that several conditions can present with a cutaneous hyperpigmentation pattern that mimics Addison disease. Agrawala et al, for example, reported a case of cutaneous hyperpigmentation in vitamin B12 deficiency masquerading as Addison disease hyperpigmentation.<sup>11</sup> In their case, however, the biopsy showed epidermal hyperpigmentation that extended from the basal layer to the stratum spinosum.

Cutaneous histopathological changes in Addison disease include an increase in the amount of melanin in basal epidermal keratinocytes, as well as a moderate amount of dermal melanophages.<sup>1,2</sup> Despite such hyperpigmentation, we found that the count of melanocytes was normal. Although the number of melanocytes per lineal millimeter of epidermis varies with the anatomical location studied as well as with the age of the individual, the percentage of melanocytes of all cells in the stratum basale normally stays over 8: in adults, it varies between 5 (vulva) and 14.6 (face and neck).<sup>12</sup> In our case, biopsies from the arm and the thigh were taken. The percentage of melanocytes in the arm in one study was 12 (with a range of 5–22.2) and in the thigh it was 8.1 (with a range of 4–16.1).<sup>12</sup> Our case was in the lowest pole of the range in the arm biopsy and much under the normality in the thigh biopsy. We have not found any previous immunohistochemical evaluation of the melanocytic population in Addison disease, although it is a well-known phenomenon that a destruction of melanocytes can happen in Addison disease.<sup>7,13</sup> In fact, Addison disease can lack cutaneous hyperpigmentation in advanced cases: Kendereški et al reported an advanced case of Addison disease without epidermal hyperpigmentation which they attributed to the high degree of melanosome degradation in secondary lysosomes (compound melanosomes).<sup>14</sup>

Our case also had pigmented granules in the luminal pole of the epithelial cells of the secretory coil of the eccrine glands. Such pigment was most likely lipofuscin, which typically accumulates in the eccrine gland with aging.<sup>15</sup> There was also iron deposit in perieccrine location which we attributed as associated to the clinical history of senile purpura, unrelated directly to the Addison disease.

In conclusion, we present the histopathological findings of one case of cutaneous hyperpigmentation associated with Addison disease in which there is hyperpigmentation of the basal layer of the epidermis with a decrease in the number of epidermal melanocytes.

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